

# Is the cerebellum relevant in the circuitry of neuropsychiatric disorders?

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Contemporary mechanistic models of several psychiatric disorders propose abnormalities in the structure and function of distinct neural networks. The cerebellum has both anatomic and functional connections to the prefrontal cortex, the subcortical limbic structures and monoamine-producing brainstem nuclei. Conspicuously, however, the cerebellum has been underemphasized in neuropsychiatric research. A growing confluence of scientific data indicate that the cerebellum may not be irrelevant, which suggests that an integrated model of neuropsychiatric disorders should include a role for the cerebellum and its relevant neural connections. This review summarizes the published data describing and characterizing the putative role of the cerebellum in normal and abnormal mood regulation, with specific attention to states of psychosis, depression and mania. The available evidence suggests that a functional role for the cerebellum should be considered in future neuropsychiatric studies.

Les modèles mécanistes contemporains de divers troubles psychiatriques mettent en cause des anomalies au niveau de la structure et de la fonction de réseaux neuronaux distincts. Le cervelet contient des connexions anatomiques et fonctionnelles avec le cortex préfrontal, les structures limbiques sous-corticales et les noyaux du tronc cérébral produisant des monoamines. Par ailleurs, il est flagrant que les recherches en neuropsychiatrie ne se sont pas suffisamment attardées au cervelet. La masse de plus en plus importante de données scientifiques convergentes indiquant que le cervelet pourrait avoir de l'importance dans ce contexte signale qu'un modèle intégré des troubles neuropsychiatriques devrait traiter du rôle du cervelet ainsi que de ses connexions neuronales pertinentes. La présente étude vise à résumer les données publiées décrivant et caractérisant le rôle présumé du cervelet dans la régulation normale et anormale de l'humeur avec accent particulier sur les états de psychose, de dépression et de manie. Les données disponibles semblent indiquer qu'il faudrait envisager le rôle fonctionnel du cervelet dans les études futures en neuropsychiatrie.

## Introduction

A comprehensive neurobiologic model for the major psychiatric disorders is not currently available. Contemporary classification systems remain symptom based, despite the growing body of literature on abnormalities in structural and functional neuroanatomy.<sup>1</sup> In the late 19th century, Babinski observed that patients with cerebellar lesions could not properly execute complex motor tasks and named the resulting condition "dysmetria." Andreasen et al<sup>2</sup> have reported that

disruption of neural circuits linking the cortex, thalamus and cerebellum (the cortico-thalamic-cerebellar-cortical circuit, or CTCCC) may presage the complex psychopathology of schizophrenia. They hypothesized that the CTCCC monitors and coordinates the fluid execution of mental activity, a process that appears to be aberrant in schizophrenia. Structural and functional cerebellar abnormalities have been described in several disorders other than schizophrenia, including anxiety disorders, depression and mania.<sup>3</sup>

We conducted a MEDLINE search of all English articles

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published between 1966 and 2004 using the key words "bipolar disorder," "depression," "schizophrenia," "cerebellum" and "cerebellar." The search was supplemented by a manual review of relevant references. Priority was given to controlled data; where such were unavailable, uncontrolled studies were included if sample size was reasonable (more than 10).

This review summarizes published data describing and characterizing the role of the cerebellum in normal and abnormal mood states, with specific attention to states of psychosis, depression and mania. We propose that the CTCCC model, heretofore applied to the pathophysiology of schizophrenia, may also be applicable to a pathophysiologic understanding of affective states and other psychiatric disorders.

## The cerebellum

### *Neuroanatomy*

The cerebellum overlies the posterior aspect of the pons and projects bidirectional fibres to brainstem structures via 3 paired peduncles. The midline (vermis) and lateral hemispheres are demarcated by fissures into smaller lobes and lobules. Inside, 4 pairs of intrinsic nuclei — dentate (most lateral), emboliform, globose and fastigial — can be found under the grey cortical mantle within a medullary core of white matter.<sup>4</sup>

Traditionally, the emphasis of studies on cerebellar function has been on the coordination of somatic motor function, control of muscle tone and equilibrium. The cerebellum, however, receives input directly or indirectly (via projections from cortical association areas and the midbrain) from nearly all sensory receptors; its output systems emanate from the cerebellar nuclei, and their influences upon cortical function are mediated primarily through brainstem nuclei at multiple levels.<sup>5</sup>

Connections between the cerebellum and the nonmotor cortical and subcortical areas have been documented through both electrophysiologic studies and anatomic tracing techniques.<sup>5</sup> The cerebellum shares bidirectional connections with a large portion of the limbic lobe and the associated subcortical nuclei, the amygdaloid complex, the septal nuclei, and various hypothalamic and thalamic nuclei, regions of interest to psychiatry through their association with emotional processing.<sup>6</sup> Furthermore, the cerebellum also communicates with the monoamine-producing brainstem nuclei, which supply the limbic system and the cerebrum with serotonin, norepinephrine and dopamine.

In animal studies, axonal transport mechanisms have been used to document synaptic contact between the fastigial nucleus of the cerebellum and the ventral tagmental area, the periaqueductal gray, the locus ceruleus and the pontine raphe.<sup>7,8</sup> Conversely, the ventral tagmental area and the mammillary body have been shown to project back to the monkey cerebellum.<sup>9,10</sup>

Functionally, electrical stimulation of the cerebellum, particularly stimulation of the vermis area 3 (V3) and the fastigial nucleus, modulates the physiology of limbic lobe struc-

tures. Evoked responses in the orbitomesial cortex, anterior cingulate gyrus, amygdala, hippocampal and dentate gyri, pyriform and preamygdaloid cortical regions and hypothalamus have been recorded through stimulation of the cerebellum.<sup>11–13</sup> Thus, the cerebellum earns its Latin name of "miniature brain," as it appears armed with the connections to "instruct" and "report" to a large proportion of the regions of the brain, including those involved in cognition, affect and mood regulation.

### *Emotional processing*

The first accounts of cerebellar atrophy and agenesis, which appeared early in the 19th century, described patients with intellectual, emotional, social and other behavioural responses that were distorted to the point of irreversible character and personality alteration.<sup>14</sup> By the mid 20th century, descriptions of dementia and psychosis in patients suffering from cerebellar degeneration began to appear,<sup>15</sup> leading Snider to hypothesize that cerebellar activity must also influence the "non-motor centres of the cerebrum."<sup>16</sup>

### *Cerebellar stimulation*

Therapeutic interventions involving the cerebellum began appearing in the 1970s, in particular the implanting of electrodes over the superior surface of the cerebellum in an attempt to control epilepsy.<sup>17</sup> In addition to improvements in seizure control, these researchers noted emotional improvements in aggression, anxiety and depression. Conversely, when recording from the cerebellar fastigial nucleus of an emotionally disturbed patient, Heath et al<sup>18</sup> described an association between increased neuronal discharges and the patient's experience of fear and anger. Similarly, when Nashold and Slaughter<sup>19</sup> stimulated the cerebellar dentate nucleus and superior cerebellar peduncle, the subject experienced an unpleasant sensation of fear. In 11 patients with severe emotional dyscontrol, the implantation of bilateral electrodes for stimulation over the superior aspect of the cerebellar cortex resulted in "extraordinary" improvements in behaviour.<sup>20</sup> Although these studies were limited in number and were not controlled, they provide evidence that direct stimulation of the cerebellum has the potential to alter moods or induce different moods in humans.

### *Cerebellar lesions*

When Schmahmann and Sherman<sup>21</sup> subsequently analyzed the behavioural impairment of 20 adult patients with lesions confined to the cerebellum, they noted that behavioural changes were most prominent in patients whose lesions were localized to the posterior lobe of the cerebellum and vermis. The clinical presentation included a combination of passivity and flattening or blunting of emotion, sometimes occurring simultaneously with disinhibited, inappropriately jocular, silly or child-like behaviour. The authors named this newly defined clinical entity "cerebellar cognitive affective syndrome" and postulated that it resulted from impaired cere-

bellar modulation of neural circuits that link prefrontal, posterior parietal, superior temporal and limbic cortices with the cerebellum.<sup>21</sup>

Interestingly, these displays of passivity and flattening or blunting of emotion and a disinhibition of restraint are phenotypically similar to the depressed and manic states in mood disorders. This presentation may also resemble some of the classical symptoms of schizophrenia, although schizophrenia is also associated with more severe cognitive impairments.

Similarly, children with mutism resulting from cerebellar tumours also display altered moods.<sup>22</sup> In particular, lesions of the vermis produced behavioural changes that extended beyond the cognitive domain, including a flattening of affect and a silly, disinhibited, regressive quality to the children's interactions, with some exhibiting a reduced tolerance of others and a general tendency to avoid physical and eye contact.

Disruption of the cerebellar circuitry may thus impair the processing of emotional responses to challenging stimuli. Furthermore, the finding that single lesions of the cerebellum can impart such a marked change in the personality of affected individuals highlights the role of cerebellar interconnectivity in affective and cognitive processing.

## Schizophrenia

### *Rationale*

Clinical observations of affective and cognitive changes arising from cerebellar lesions and stimulation permit the hypothesis that the cerebellum may not be irrelevant in some neuropsychiatric states.<sup>23</sup> There is evidence that patients with schizophrenia have an altered corticocerebellar connectivity.<sup>2,24</sup> Andreasen et al<sup>2</sup> and Wiser et al<sup>24</sup> proposed that disruption of the CTCCC may underlie the combination of symptoms observed in schizophrenia. Analogous to the cerebellar role in facilitating rapid and smooth execution of motor tasks, they further proposed that the CTCCC performs a similar function in the monitoring and coordination of the fluid execution of mental activity resulting in normal cognitive function. Conversely, disruption in the activity of this circuit leads to the disordered cognition and clinical symptoms characteristic of schizophrenia.<sup>25</sup>

### *Structural neuroimaging studies*

During the 1980s and early 1990s, with the growing availability of computed tomography (CT), reports of cerebellar vermal atrophy or hypoplasia in patients with schizophrenia began appearing in the literature,<sup>26–28</sup> although such reports could not be confirmed by others<sup>29</sup> (Table 1).

Structural magnetic resonance imaging (MRI) analyses using quantitative anthropometric techniques have yielded more consistent reports of cerebellar atrophy in schizophrenia,<sup>30,32,33,35</sup> with some authors attempting to delineate a subset of patients with reduced or atrophied cerebella. Global reductions in cerebellar volume have been associated specifically with perinatal brain insults,<sup>31</sup> schizophrenia in men,<sup>37</sup> child-

hood-onset schizophrenia,<sup>39</sup> very-late-onset schizophrenia,<sup>36</sup> chronic schizophrenia<sup>32</sup> and psychotic symptoms.<sup>48</sup> Other authors have noted atrophy delimited to the vermis.<sup>33,35,37</sup>

As was the case with CT studies, not all investigators using MRI have found reduced cerebellar volumes in schizophrenia. Some have reported a larger vermis in the brains of patients with schizophrenia,<sup>34</sup> as well as increased grey matter.<sup>38</sup> Other MRI studies have failed to locate any consistent change in the cerebellar structure in schizophrenia.<sup>49</sup>

Although the structural mapping studies have been equivocal, the weight of evidence supports extending the study of cerebellar activity in schizophrenia. For example, the finding that unaffected first-degree relatives of probands with schizophrenia have reduced cerebellar volumes,<sup>50</sup> along with the observation of reduced cerebellar volumes in neuroleptic-naïve patients with schizophrenia,<sup>35</sup> suggests that cerebellar atrophy may be a hereditary trait rather than a psychotropic-associated epiphenomenon.

### *Functional imaging studies*

Results from memory tasks involving both words and faces in patients with schizophrenia provide further support for the CTCCC model. The CTCCC regions that are activated in healthy control subjects during recall (the prefrontal, thalamic and cerebellar areas) displayed less or no activation in patients with schizophrenia. Recent functional MRI (fMRI) investigations using a variety of additional cognitive tests (Wisconsin Card Sorting Test,<sup>41</sup> Working Memory [n-back] Task<sup>42</sup> and Periodic Sequence-Learning Task<sup>43</sup>) have similarly reported decreased activation of the cerebellum (Table 1).

Differences in cerebellar perfusion between patients with schizophrenia and control subjects have been noted even in the absence of cognitive or affective challenges. These results may be reversible, with a decrease in cerebellar blood perfusion<sup>46</sup> and activation<sup>47</sup> after administration of atypical antipsychotics. Reports of aberrant cerebellar activity, with concomitant medication effects, suggests that disturbances in cerebellar activation, and concomitant changes in blood volume and perfusion, are partly state, partly trait and partly medication mediated. Future investigations should strive to further delineate and characterize the relative influence of each factor.

### *Cellular abnormalities in the cerebellum*

Postmortem studies have also revealed altered cerebellar structure, specifically a smaller anterior vermal lobe,<sup>51</sup> which appears to correlate with occipital asymmetry.<sup>52</sup> Postmortem analyses of cerebellar cytoarchitecture have revealed a reduction in the density of vermal Purkinje cells in the brains of patients with schizophrenia<sup>53</sup> and, more recently, a reduction in the size of the Purkinje cells,<sup>54</sup> although other investigators have failed to replicate these results.<sup>55</sup>

At the subcellular level, evidence is accumulating that cerebellar abnormalities in schizophrenia might arise from impaired synaptic architecture.<sup>56–60</sup> Synaptophysin, complexin I and complexin II are integral proteins in the construction of

functional synapses; as such, a reduction in their expression has been taken as indicative of impaired synaptic connectivity. Whereas synaptophysin is found in both inhibitory ( $\gamma$ -aminobutyric acid [GABA]-ergic) and excitatory (glutamatergic) synapses, complexin I prefers the former and complexin II associates preferentially with the latter. On the basis of the finding that mRNA and protein levels of synaptophysin and complexin II, but not complexin I, were reduced, the authors proposed that it was the excitatory neurons in the cerebellum, in particular, that were affected by or responsible for the observed cerebellar phenotypes in schizophrenia.<sup>57</sup> However, there is also evidence that inhibitory neurotransmission is impaired, for example, reports that both reelin, a glycoprotein secreted preferentially by GABAergic interneurons, and glutamic acid decarboxylase, a prerequisite enzyme for GABA synthesis, were reduced in the cerebellum of patients with schizophrenia.<sup>56</sup> The concept of impaired cerebellar synapse formation in schizophrenia is further supported by

findings of reduced levels of synaptosomal-associated protein 25 (SNAP-25, a synaptic protein involved in the docking of synaptic vesicles) against a background of unaffected levels of cytoskeletal proteins.<sup>59</sup> Perhaps the underlying source of impaired synaptogenesis is an increase in expression of an axonal chemorepellant, such as semaphorin 3A. Comparing gene expression in the cerebellum of patients with schizophrenia and healthy subjects, Eastwood et al<sup>60</sup> showed that this particular chemorepellant is elevated in expression and is associated with the downregulation of genes involved in synaptic formation and maintenance in the brains of patients with schizophrenia.

## Major depressive disorder

Using a positron emission tomography analysis of regional blood flow, Reiman et al<sup>61</sup> investigated the neuroanatomic correlates of externally generated emotions. These authors

**Table 1: Neuroimaging studies of the cerebellum in schizophrenia**

Study	Subjects	Procedure	Results
<b>Structure</b>			
Weinberger et al <sup>27</sup>	35 SZFE, 17 SZC, 23 AD, 27 OP, 26 HC	CT	Cb atrophy 12% (SZC), 9% (AD) >> OP, SZFE, HC
Nasrallah et al <sup>26</sup>	55 SZ, 24 BPM, 27 HC	CT	Cb atrophy: BPM > SZ > HC
Lippmann et al <sup>28</sup>	54 SZ, 18 BPV, 79 HC	CT	CbV: SZ, BPV < HC
Yates et al <sup>29</sup>	108 SZ, 50 AD, 74 HC	CT	No differences noted in CbV, CbH or CbT
Uematsu and Kaiya <sup>30</sup>	40 SZ, 17 HC	MRI	No differences, but CbV size predicted response
Nasrallah et al <sup>31</sup>	30 SZ	MRI	↓ CbV associated with perinatal brain injury
DeLisi et al <sup>32</sup>	50 SZ, 20 HC	MRI	↑ rate of shrinkage of R CbH (SZ v. HC)
Nopoulos et al <sup>33</sup>	65 SZ, 65 HC	MRI	↓ CbV (SZ v. HC)
Levitt et al <sup>34</sup>	15 SZ, 15 HC	MRI	↑ CbV (SZ v. HC)
Ichimiya et al <sup>35</sup>	20 SZNN, 20 HC	MRI	↓ CbV (SZNN v. HC)
Barak et al <sup>36</sup>	21 VLOSZ, 21 HC	CT	↑ Cb atrophy (VLOSZ v. HC)
Okugawa et al <sup>37</sup>	30 SZC, 18 HC	MRI	↓ CbV (SZC v. HC) in men only
Suzuki et al <sup>38</sup>	45 SZ, 42 HC	MRI	↑ Cb GM (SZ v. HC)
Keller et al <sup>39</sup>	50 SZ, 50 HC	MRI	↑ loss of CbT during adolescence (SZ v. HC)
<b>Function: challenge</b>			
Andreasen et al <sup>2</sup>	14 SZ, 13 HC	<sup>15</sup> O PET	PFC-Th-Cb network visible for HC, absent for SZ
Crespo-Facorro et al <sup>40</sup>	14 SZ, 13 HC	<sup>15</sup> O PET	Novel memory task: ↓ CbT (SZ v. HC) Recalling practised words: ↓ L CbH (SZ v. HC)
Riehemann et al <sup>41</sup>	9 SZNN, 9 HC	fMRI	Wisconsin Card Sorting: ↓ Cb (SZNN v. HC)
Meyer-Lindenberg et al <sup>42</sup>	13 SZMF, 13 HC	fMRI	Working memory activation: CbT, PHc (SZMF) v. dIPFC, ACC (HC)
Kumari et al <sup>43</sup>	6 SZ, 6 HC	fMRI	Procedural learning: Cb activated in HC, but not in SZ
<b>Function: rest</b>			
Loeber et al <sup>44</sup>	10 HC, 10 BPV, 10 SZ	DSC fMRI	CbT blood volume: BPV > HC > SZ
Kim et al <sup>45</sup>	30 SZ, 30 HC	<sup>15</sup> O PET	CbT CBF: SZ > HC
Miller et al <sup>46</sup>	30 SZMF ⇒ SZAA*	<sup>15</sup> O PET	With risperidone: ↑ CbT
Stephan et al <sup>47</sup>	6 SZMF ⇒ SZAA*, 6 HC	fMRI	With olanzapine: ↑ R CbH (SZAA)

Note: ACC = anterior cingulate cortex; AD = affective disorders; BPM = bipolar disorder — manic; BPV = bipolar disorder — varied (all phases of illness); Cb = cerebellum; CBF = cerebral blood flow; CbH = cerebellum hemisphere; CbT = cerebellum total; CbV = cerebellum vermis; CT = computed tomography; dIPFC = dorsolateral prefrontal cortex; DSC-fMRI = dynamic susceptibility contrast fMRI; fMRI = functional MRI; GM = gray matter; HC = healthy control; L = left; MRI = magnetic resonance imaging; OP = psychiatric disorder, not affective, not schizophrenic; PET = positron emission tomography; PFC = prefrontal cortex; PHc = parahippocampal cortex; R = right; SZ = schizophrenia; SZAA = schizophrenia — treated with atypical antipsychotic; SZC = schizophrenia — chronic; SZFE = schizophreniform — first episode; SZMF = schizophrenic — medication free; SZNN = schizophrenic — neuroleptic naïve; Th = thalamus; VLOSZ = very late onset schizophrenia.

\*Patients were scanned twice, first when medication free, then while undergoing treatment with atypical antipsychotics.

imaged the brains of healthy volunteers as they watched film clips designed to evoke a variety of emotional states, including happiness, sadness and disgust. In addition to finding activation of the limbic and paralimbic areas, the group noted activation of the cerebellar hemispheres. Using a similar technique, Lane et al<sup>62</sup> extended these results by demonstrating that sadness, but not happiness, increased activation of the anterior cerebellar vermis.

In contradistinction to the relevant body of morphometric studies examining cerebellar structure in schizophrenia, there are very few studies examining cerebellar size in unipolar depression. Early MRI studies<sup>63,64</sup> showed reduced cerebellar size in patients with unipolar depression, whereas a more recent quantitative MRI investigation failed to find any statistically significant differences.<sup>65</sup> The most recent MRI investigation<sup>65</sup> did reveal, however, that in patients who did not respond to fluoxetine treatment, total cerebellar tissue volume decreased as baseline depression scores increased (Table 2).

In an effort to discern the differential brain activation pattern that results from evoking sadness in healthy control subjects and patients with unipolar depression, Beauregard et al<sup>68</sup> performed fMRI scans while both groups viewed an emotionally laden film. Transient sadness produced significant activation in both groups, not only in the medial and inferior prefrontal cortices and the middle temporal cortex, but also in the cerebellum. Furthermore, the patients with depression displayed greater activation of the left medial prefrontal cor-

tex and the right anterior cingulate gyrus, but less activation of the cerebellum.

In a positron emission tomography investigation, cerebral blood flow was compared in subjects with acute depression and healthy controls, before and after a transient mood challenge. In line with the results obtained with fMRI, the patients with depression displayed less activation of the cerebellum and thalamus.<sup>70</sup>

To test whether subjects who recover from depression show abnormal brain activity, Smith et al<sup>69</sup> acquired fMRI data during a conditioning paradigm with a noxious pain stimulus. Although similar patterns of brain activation during painful stimulation were found for both patients and healthy controls, subjects who had recovered from depression displayed less cerebellar activation than the control subjects during anticipation of the noxious stimulus. These findings suggest that depression may impart a permanent and irreversible change in cerebellar function.

These findings of cerebellar hypoactivity in response to an emotional challenge are comparable to reduced cerebellar activation to cognitive challenges in schizophrenia.<sup>41-43</sup> This apparent reduction in cerebellar dynamic range may result if the cerebellum is tonically hyperactive and thus near the ceiling of maximal activation. Dolan et al<sup>78</sup> were the first to report an increase in baseline cerebellar vermal blood flow in a subset of patients with depression and cognitive impairment. More recent data suggest that this tonic increase in cerebellar

**Table 2: Neuroimaging studies of the cerebellum in mood disorders**

Study	Subjects	Procedure	Unipolar	Bipolar
<b>Structure</b>				
DeBello et al <sup>66</sup>	30 BPM, 15 HC	MRI		↓ V3 (BPM v. HC)
Brambilla et al <sup>67</sup>	22 BPV, 22 HC	MRI		↓ CbT (BPF v. HC)
Shah et al <sup>63</sup>	27 MDD, 36 HC	MRI	↓ CbV (MDD v. HC)	
Escalona et al <sup>64</sup>	30 MDD, 35 HC	MRI	↓ CbT (MDD v. HC)	
Pillay et al <sup>65</sup>	38 MDD, 20 HC	MRI	↔ CbT (MDD v. HC)	
<b>Function: challenge</b>				
Beauregard et al <sup>68</sup>	7 MDD, 7 HC	fMRI	↓ L CbH (MDD v. HC)	
Smith et al <sup>69</sup>	10 MDE, 8 HC	fMRI	↓ CbT (MDE v. HC)	
Liotti et al <sup>70</sup>	10 MDE, 7 MDD, 8 HC	<sup>15</sup> O PET	↓ CbT (MDE, MDD v. HC) ↓ CbV (MDE v. MDD)	
Curtis et al <sup>71</sup>	5 BPV, 5 SZ, 5 HC	fMRI		↑ CbV (BPV v. HC, SZ)
Kruger et al <sup>72</sup>	9 BPE, 11 BPD	<sup>15</sup> O PET		↓ CbV (BPD v. BPE) ↑ R Cb (BPE v. BPD)
<b>Function: rest</b>				
Videbech et al <sup>73</sup>	42 MDD, 47 HC	<sup>15</sup> O PET	↑ CbT (MDD v. HC)	
Kimbrell et al <sup>74</sup>	38 MDV, 37 HC	<sup>18</sup> FDG PET	↑ R, L CbH (MDD v. HC) ↑ CbV (MDD v. MDE)	
Ketter et al <sup>75</sup>	43 BPV, 43 HC	<sup>18</sup> FDG PET		↑ CbT (BPV v. HC) ↔ Cb (BPD v. BPE)
Osuch et al <sup>76</sup>	25 MDD, 27 BPD	<sup>18</sup> FDG PET	↑ L Cb (BPD v. MDD)	
Davies et al <sup>77</sup>	7 MDD ⇒ MDE*	<sup>99m</sup> Tc SPECT	↑ R Cb (MDD v. MDE)	

Note: BPD = bipolar disorder — depressed; BPE = bipolar disorder — euthymic; BPF = bipolar disorder — familial; BPM = bipolar disorder — manic; BPV = bipolar disorder — varied (all phases of illness); Cb = cerebellum; CbH = cerebellum hemisphere; CbT = cerebellum total; CbV = cerebellum vermis; FDG = fluorodeoxyglucose; fMRI = functional MRI; HC = healthy control; L = left; MDD = major depressive disorder — depressed; MDE = major depressive disorder — euthymic; MDV = major depressive disorder, various severities of depression; MRI = magnetic resonance imaging; PET = positron emission tomography; R = right; SZ = schizophrenia; SPECT = single-photon emission computed tomography; V3 = vermis area 3; ↔ = no differences.

\*Patients were scanned twice, before and after treatment of acute depression.



activity is characteristic of major depression, regardless of mood state or medication history.<sup>73,74</sup>

Similar to the findings in schizophrenia, in which cerebellar blood flow decreases following antipsychotic treatment,<sup>44,46</sup> an association between successful treatment of depression and a decrease in cerebellar perfusion has been reported.<sup>77</sup> Thus, a positive treatment outcome in patients with both mood and psychotic disorders may be associated with a reduction in cerebellar activity and blood flow (Table 2).

Preliminary studies appear to indicate that patients with unipolar depression and schizophrenia may share similar structural (volumetric reductions) and functional (baseline hyperactivity) abnormalities in the cerebellum. However, the available results from investigations in unipolar depression are extremely limited and prevent definitive conclusions. Moreover, the high prevalence of depressive symptoms among people with schizophrenia<sup>79</sup> may account for some of the observed similarities. Future imaging investigations should strive to clarify the role of cerebellar structural and functional abnormalities in unipolar depression, and their relation to clinical outcomes and changes in metabolism.

## Bipolar disorders

Because cerebellar atrophy has been documented in depression and schizophrenia, it is important to investigate the structural and functional aspects of the cerebellum in bipolar disorders.<sup>68</sup> An early report of cerebellar atrophy in mania<sup>80</sup> was followed by several studies confirming this initial observation.<sup>26–28</sup> In 2 of the 3 studies,<sup>27,28</sup> which controlled for alcohol use in both patient and healthy control groups, atrophy of the vermis was reported, whereas Dewan et al<sup>81</sup> were not able to find any differences in cerebellar atrophy or cerebellar grey and white matter densities.

A subsequent MRI investigation of the cerebellum in patients with bipolar disorder did not reveal any gross morphologic differences between the patient group and healthy controls.<sup>66</sup> However, when the patients with bipolar disorder were subdivided into first-manic-episode and multiple-manic-episode groups, the researchers found that the V3 region was significantly smaller in the multiple-episode group. Further analysis revealed that among multiple-episode patients it was the number of previous depressive episodes, not substance abuse or duration of lithium exposure, that contributed to the reduction in V3 volume.<sup>66</sup>

The only other morphometric MRI study examining the cerebellum in bipolar disorder<sup>67</sup> did not reveal any statistically significant difference in total cerebellar or vermal size between patients with bipolar disorder and healthy controls. However, the authors did find a smaller vermis in patients with at least 1 first-degree relative possessing a history of mood disorders. Furthermore, there was a significant trend for an inverse correlation between number of prior affective episodes and size of the V3 region. These results corroborate the earlier MRI finding,<sup>66</sup> leading to the possibility that atrophy of this particular region of the vermis may be associated with duration or course of illness.<sup>67</sup>

Loeber et al<sup>44</sup> employed dynamic susceptibility contrast

MRI and reported that patients with bipolar disorder have lower cerebellar blood volumes than healthy controls and patients with schizophrenia, even after adjustment for anatomic volume differences. The cerebellar region reported most frequently in neuroimaging studies of patients with bipolar disorder, the vermis, showed the largest reduction in blood volume. With atypical antipsychotic medication, however, this relative decrease in blood volume appeared to show a reversal toward age- and sex-matched norms.<sup>82</sup>

In another study, Kruger et al<sup>72</sup> investigated blood flow changes in patients with bipolar disorder (both with depression and in remission) and in healthy individuals during a sadness induction protocol. Baseline differences were noted between the 2 groups, with the bipolar cohort displaying less cerebellar blood flow. Interestingly, when challenged with the sadness induction protocol, different, nonoverlapping regions of the cerebellum were activated in the 2 groups; specifically, among the patients with bipolar disorder, a greater fraction of cerebellar tissue was activated.

In contrast to findings of decreases in blood volume and flow, Ketter et al<sup>75</sup> reported increases in metabolism in the cerebellar and posterior cortical areas, occurring independently of illness phase, in a relatively large study of treatment-resistant patients with bipolar disorder.

Preliminary investigations into cerebellar structure and function in bipolar disorder have consistently noted differences relative to healthy control subjects; however, definitive conclusions are not yet possible. Provisional studies have reported a smaller cerebellum, with decreased blood volume and increased glucose metabolism. Seemingly discrepant findings of decreased blood volume and increased glucose metabolism may reflect the clinical heterogeneity of the bipolar populations studied. Thus, it may be possible that cerebellar hypermetabolism is a finding particular to treatment-resistant subjects with bipolar disorder.

In summary, preliminary results in patients with unipolar and bipolar depression suggest aberrant cerebellar function and, possibly, size. The studies indicate that both patient populations may have abnormalities in cerebellar function under both baseline and challenge conditions. Given the small number and inadequate replication of these studies, caution should be exercised in interpreting their results.

## Summary and discussion

Results from a number of neuropsychiatric investigations have documented abnormalities in cerebellar function and structure. Moreover, pharmacologic and psychosocial therapeutic interventions for patients with these disorders have been reported to coincide with changes in cerebellar function. Recent scrutiny of the cerebellum in neuropsychiatric investigations has been facilitated by technologic advances in imaging instruments that were formerly (in the mid to late 1990s) unable to fully capture the cerebellum. A growing awareness of the putative role of the cerebellum in higher cognitive function has promoted the practice of using this brain region for standardizing global brain activity.

The finding of simultaneous alteration in activation of the

cerebellum, the thalamus and parts of the frontal cortex has led some authors to propose the CTCCC model to explain the diverse symptoms of schizophrenia. Thus, reduced "monitoring" of cortical activity by the cerebellum may initiate a dysregulation of certain neural circuits involved in emotional and cognitive function. It remains possible that overlapping aberrations in cerebellar function could contribute to the phenomenology observed in mood disorders. Research into the putative cerebellar role in mood disorders has been conspicuously absent.

The analysis of gene expression in the cerebellum is allowing researchers to look at cellular changes that accompany psychiatric illnesses at the molecular levels. The results of altered cerebellar gene expression in psychiatric illnesses will invite the study of genetic polymorphism in the general population, allowing an endophenotypic classification of psychiatric conditions. Basic research on the cellular pathways at work in the cerebellum also offers additional insight in the search for novel targets for pharmacologic intervention. Putative models of neural networks implicated in the pathophysiology of mood disorders<sup>83</sup> and schizophrenia<sup>47</sup> provide a neuroanatomic framework for such future endeavours.

It is tempting to speculate that atrophy of the cerebellum may be a nonspecific response to psychologic stress. After reporting altered resting blood flow to the vermis in adolescents with prior childhood sexual abuse, Anderson et al<sup>84</sup> proposed that early trauma may interfere with the development of the vermis, producing neuropsychiatric symptoms more commonly observed with drug use. Like the hippocampus, the vermis has a protracted period of postnatal development and may produce granule cells postnatally.<sup>85</sup> Since the vermis has the highest density of glucocorticoid receptors during development,<sup>86</sup> even exceeding that of the hippocampus, it may be particularly vulnerable to the effects of stress hormones,<sup>87</sup> which are frequently elevated in subjects with psychiatric conditions.<sup>88</sup>

To recapitulate, an ideal model for neuropsychiatric disorders does not exist. With minimal equivocation, current models fall short of providing a comprehensive explanation for the diverse phenomenology observed in persistent mental illness such as mood and psychotic disorders. It is possible that cerebellar abnormalities noted in the extant literature are epiphenomena relating to abnormalities elsewhere. The alternative hypothesis, that the cerebellum may be relevant secondarily or play an integral role in aberrant neural network systems, remains to be confirmed or refuted.

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